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(12) UK Patent Application (19) GB (11) 2 023 000 A

(21) Application No 7827189
(22) Date of filing 17 Jun 1978
(23) Claims filed 17 Jun 1978
(43) Application published 28 Dec 1979
(51) INT CL[2] A61K 9/06 31/405
(52) Domestic classification A5B 170 232 23Y 351 352 35Y 381 38Y 392 402 40Y 411 41Y 441 44Y 480 482 483 48Y 523 52Y 551 55Y 575 57Y 586 58Y 616 61Y 664 66Y 826 J L
(56) Documents cited GB 1316556
(58) Field of search A5B
(71) Applicants Kowa Company Limited, No. 6-29, Nishiki 3-chome, Naka-ku, Nagoya-shi, Japan.
(72) Inventors Hidetaka Nagai Toyojiro Muramatsu Toshio Inagi
(74) Agents G.F. Redfern & Co.

(54) Antiinflammatory analgesic gelled ointments

(57) An antiinflammatory analgesic gelled ointment comprises indomethacin, a medium consisting of a glycol, alcohol and water, a gelling agent selected from cellulose derivatives and carboxyvinyl polymers which have been neutralised with amines, and water.

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Method

A) Swell 1) in 20 g of water.
B) Dissolve 2) in a mixture of 3) and 4).
C) Add B) and A) and mix until the mixture is completely hydrated.
D) Dissolve 5) in 10 g of water. Add the mixture to C) with stirring. Bring the resultant mixture to the final weight with further water and form the composition by mixing until it becomes homogeneous.

EXAMPLE 3

Materials

1) Carboxyvinyl polymer	1.0 g
2) Indomethacin	1.0 g
3) Propylene glycol	12.0 g
4) Ethanol	30.0 g
5) Diisopropyl adipate	2.0 g
6) Diisopropanolamine	1.1 g
7) Purified water	An amount sufficient to bring the final weight to 100 g.

Method

A) Swell 1) in 20 g of water.
B) Dissolve 2) in a mixture of 3), 4) and 5).
C) Add B) to A) and mix until the mixture is completely hydrated.
D) Dissolve 6) in 10 g of water. Add the mixture to C) with mixing. Bring the resultant mixture to the final weight with further water and form the composition by mixing until it becomes homogeneous.

EXAMPLE 4

Materials

1) Carboxyvinyl polymer	1.0 g
2) Hydrocyethyl cellulose	1.0 g
3) Indomethacin	1.0 g
4) Polyethylene glycol 300	10.0 g
5) Ethanol	30.0 g
6) Diisopropyl adipate	2.0 g
7) Diisopropanolamine	0.9 g
8) Purified water	An amount sufficient to bring the final weight to 100 g.

Method

A) Swell 1) and 2) in 20 g of water.
B) Dissolve 3) in a mixture of 4), 5) and 6).
C) Add B) to A) and mix until the mixture is completely hydrated.
D) Dissolve 7) in 10 g of water. Add the mixture to C) with mixing. Bring the resultant mixture to the final weight with further water and form the composition by mixing until it becomes homogenous.

EXAMPLE 5

Materials

1) Hydroxypropyl cellulose	5.0 g
2) Indomethacin	0.5 g
3) Propylene glycol	20.0 g
4) Triethanol amine	0.35 g
5) Ethanol	30.0 g
6) Purified water	An amount sufficient to bring the final weight to 100 g.

Method

A) Swell 1) in 20 g of water.
B) Dissolve 2) in a mixture of 3) and 5).
C) Dissolve 4) in the remaining water.
D) Add A) and C) to B), and stir the resultant mixture until it becomes homogeneous.

EXAMPLE 6

Inhibitory Effect on Carrageenan-induced Edema:

Wister male rats each weighing about 200 g; arranged in groups each consisting of six rats, were given subcutaneously 0.05 ml of a 1% carrageenan solution on their hind right paws. Immediately, about 100 mg of an ointment prepared as in Example 1 was coated onto each injected region which was covered with a polyethylene film and held thereon with gauze. Two hours later, the polyethylene film and gauze were removed. One hour after such removal, the weight of edema was measured. The control group was coated only with the ointment base and thereafter treated in the same manner as in the test groups. The results obtained are as shown in Table 1.

Table 1

Agent	Weight of edema (g) MEAN ± ERROR	Inhibition Ratio (%)
Control	0.50 ± 0.03	
Indomethacin ointment (1%)	0.35±0.04	31.1*

* $p < 0.05$

EXAMPLE 7

Inhibitory Effect on Acceleration of Blood Vessel Permeability:

Guinea pigs were coated twice with about 50 mg of the ointment prepared as in Example 1 on the skin of their backs after the hair had been removed at an interval of 1 hour. One hour after the second coating, a 1% Evans Blue solution was injected intravenously, and immediately 10 µg of a histamine hydrochloride solution was intradermally injected into each ointment-coated region. 30 minutes later, the animals were depleted to death. Each skin dyed blue was exfoliated, and the pigment was extracted with pyridine and

determined; the control group was coated only with the ointment base and thereafter treated in the same manner as the test groups.

The results obtained are as shown in Table 2.

Table 2

Agent	Evans' Blue ug/region Mean ± error	Inhibition Ratio (%)
Control	246.2 ± 26.5	-
Indomethacin ointment (1%)	202.8 ± 28.1	17.6

EXAMPLE 8

Absorption from Skin:

Guinea pigs were coated with about 1 g of the ointment prepared as in Examples 1 and 3 and suspended with about 0.1 g of the ointment on the skin of the back over a region of 2 × 2 cm from which the hair was removed, one day after cutting of the hair. At the fifth hour after coating, the preparation was recovered and the absorption ratio was calculated from the recovered amount.

The result obtained is shown in Table 3.

TABLE 3

Test Compound	Cream*	Ointment in Example 1	Ointment in Example 3
Absorption ratio after 5 hours (%)	6.0 ± 2.0	13.4 ± 2.6	25.5 ± 1.1

*prepared according to the method reported in Europ. J. Pharmacol., *3*, 157 - (1968).

EXAMPLE 9

The clinical effects of 84 cases collected from three establishments are shown in Table 4. In this Table, the percentage values are given in brackets.

Table 4

	Excellent	Good	Fair	Ineffective	Aggravation	Unknown	Total
Distrosion	1	8	2	2	0	0	13
Contusion	0	7	0	2	0	0	9
Fracture, dislocation and sequelae	0	2	4	1	0	0	7
Traumatic arthritis	0	1	2	1	0	0	4
Total	1 (3.0)	(54.5)	8 (24.2)	6 (18.2)	0	0	33
Arthrosis deformans	0	3	10	4	0	0	17
Myositis		2	0	1	0	0	3
Total	0	10 (23.8)	19 (45.2)	12 (28.6)	0	1 (2.4)	42
Following post operative	0	3	2	1	0	0	6
[illegible]	1	0	1	1	0	0	3
Total	2 (2.4)	31 (36.9)	30 (35.7)	20 (23.8)	0	1 (1.2)	84

CLAIMS

1. An antiinflammatory analgesic ointment comprising indomethacin, a medium therefor comprising a glycol, an alcohol and water, and a gelling agent selected from cellulose derivatives and carboxyvinyl polymers which have been neutralised with an amine, the amount of water present being sufficient to produce a gel of a required consistency.

2. An ointment as claimed in Claim 1, which further includes an adjuvant to increase absorption of the indomethacin in use.

3. An ointment as claimed in Claim 1 or Claim 2, wherein said indomethacin is present in an amount of 0.5 to 1.5% by weight of the ointment.

4. An ointment as claimed in any one of Claims 1 to 3, wherein said glycol is propylene glycol, butylene glycol, or polyethylene glycol.

5. An ointment as claimed in any one of the preceding Claims, wherein said medium comprises 5 to 35% by weight of the glycol, 10 to 50% by weight of the alcohol and 30 to 50% by weight of water.

6. An ointment as claimed in any one of the preceding Claims, wherein said cellulose derivative is hydroxyethyl cellulose, methyl cellulose, carboxymethyl cellulose, or hydroxypropyl cellulose.

7. An ointment as claimed in any one of the preceding Claims, wherein said gelling agent is present in an amount of 0.5 to 5% by weight of the ointment.

8. An ointment as claimed in Claim 2 or any of Claims 3 to 7 as appendent thereto, wherein said adjuvant is a C_1 - C_5 alcohol ester of a C_1 - C_{14} monocarboxylic acid or a C_1 - C_3 alcohol ester of a C_4 - C_{10} dicarboxylic acid.

9. An ointment as claimed in Claim 2 or any of Claims 3 to 8 as appendent thereto, wherein said adjuvant is present in an amount of 0.5 to 5% by weight of the ointment.

10. An antiinflammatory analgesic ointment substantially as hereinbefore described with reference to any of Examples to 1 to 5.

Printed for Her Majesty's Stationery Office, by Croydon Printing Company Limited, Croydon Surrey, 1979
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

COMPOUNDERS' CORNER

By Loyd V. Allen, Jr., Pharmacist
M. Lou Stiles, Pharmacist

The Compounders' Corner is a new column for the Missouri Pharmacist, written by two faculty members of the Pharmaceutics Section of the University of Oklahoma College of Pharmacy. Both also work part-time in community pharmacies.

Loyd V. Allen, Jr., Ph.D., is professor and head of the Pharmaceutics Section and director of the Drug Analysis Laboratory at University of Oklahoma. M. Lou Stiles is Associate Professor and Director of Formulations Service (Pharmaceutics, Hospital Pharmacy, Sterile Products).

Allen and Stiles are writing the column because "for the past several years there has been a gradual de-emphasis of pharmaceutical formulation expertise, both in the pharmacy literature and in the curricula of most of our colleges of pharmacy. Nonetheless, we constantly receive inquiries concerning formulation problems encountered in the practice settings, both community and hospital. In fact, the number of inquiries has been increasing in the past year. It is because of these inquiries that we decided to share some of the formulations being compounded, and at the same time, invite practitioners to send in their prescriptions to us so that we can continue to report this activity."

Remember, the column is a report of compounding activities. You should use your own professional judgment as whether to use these formulations in your practice.

If you have formulations you want to share with the authors, send them to Compounders' Corner, c/o Missouri Pharmacist, 410 Madison St., Jefferson City, MO 65101.

Minoxidil Gel:

Rx	Minoxidil	2%
	Carbopol 934	2%
	Water	10%
	Ethanol q.s.	87%

Preparation:

If the minoxidil is obtained from the commercially available tablets, it must be extracted by pulverizing the tablets and then adding this obtained p wder to Alcohol, USP. After mixing for about five minutes, filt r the mixture to obtain the minoxidil as a clear alcoholic solution.

The remaining amount of alcohol can now be added to this filtrate.

If the minoxidil is obtained as a plain powder, it can be dissolved in the required amount of Alcohol, USP.

The minoxidil solution is then placed in a suitable container and the Carbopol 934 added with constant agitation until a uniform mixture is obtained and all of the polymer is dispersed. The water is added with continued mixing. The final product is allowed to stand for at least one hour for thorough hydration of the polymer.

Use:

Minoxidil Gel is used as an agent purported to encourage growth of hair. (NOTE: This is not an endorsement of the use of this product for this indication.)

Packaging:

This product should be packaged in air-tight containers to prevent the evaporation of the ethanol. A nice package is obtained by using plastic dropper containers. The product is sufficiently fluid to be easily squeezed out of these containers.